REMARKS

Applicant noted with appreciation that the Examiner has withdrawn the rejections presented in the Office Action mailed November 4, 2004.

Claims 31-35, 40-42, 51, 58-62, 67-69, and 78 were pending.

Claims 31, 41, 42, 51, 58, 68, 69, 78 have been amended. Claims 97 and 98 have been added. Upon entry of these amendments, claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-98 are pending and under consideration.

I. CLAIMS AMENDMENTS

Claims 31 and 58 have been amended to specify the group of diseases which may be treated using the claimed method. Support for these amendments can be found throughout the specification.

Claims 41, 42, 68 and 69 have been amended for clarity.

Claims 51 and 78 have been amended to establish a proper antecedent basis from their base claims.

New claims 97 and 98 are drawn to the use of the claimed method to treat a metabolic disorder related to an α-galactosidase A deficiency in humans and animals. Support for the new claims can be found, for example, on page 3, lines 20-21 and on page 7, lines 10-11 of the specification.

Thus, these amendments do not introduce new matter. Accordingly, entry thereof is respectfully requested.

II. REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH

Claims 31-35, 40-42, 51, 58-62, 67-69 and 78 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement by containing subject matter which was not described in the specification in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/or use the invention commensurate in scope with these claims. In particular, the Examiner alleges that the instant specification does not provide any working examples supporting a method for treating a disease or any symptoms of a disease. Reconsideration is respectfully requested in view of the proposed amendments to the claims.

Applicant has amended claims 31 and 58 to define a condition treatable by the claimed method. Thus, amended claims 31 and 58 recite in pertinent part: "A method for treatment of

a metabolic disorder or condition related to an α-galactosidase A deficiency, said method comprising...".

Applicant respectfully submits that the specification and the amended claims are fully enabling to one of skill in the art to use the method for treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency without undue experimentation for the following reasons.

The instant specification provides an extensive disclosure of all of the elements of the claimed methods. The compositions to be used in accordance with the claimed methods are fully enabled by the instant specification, including the expression cassette, the myosin enhancer, the promoters, the polynucleotide sequences of interest and the vector (see, *e.g.*, pages 3-7 of the specification).

Further, the specification provides an ample description of how the compositions of the invention were used by the way of working examples. In particular, the examples demonstrated the effect of muscle-specific regulatory elements on the expression of human α-galactosidase (see, *e.g.*, Table 1 on page 12 of the specification) and the enhanced expression of the human α-galactosidase in the culture medium of the pX3F-, pX4F- or pX7F-transfected myoblasts (see, *e.g.*, page 13, line 16 through page 14, line 7 of the specification). It is noteworthy that these experiments were the first report in which a correctly glycosylated form of human α-galactosidase was expressed and secreted from differentiated muscle cells.

Based on aforementioned, Applicant respectfully submit that the instant specification is fully enabling for a skilled artisan to make and use the invention without undue experimentation and commensurate in scope with the amended claims. "The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art." *See*, MPEP § 2140. Thus, the enablement requirement is satisfied.

Further, the Examiner alleges that the instant specification does not provide any correlation between the expression levels of alpha-galactosidase in the Fabry-diseased mice and alleviation of the symptoms of the disease. This rejection is traversed. Reconsideration is respectfully requested.

It is well-known in the art that elevated levels of α-galactosidase A have positive effect in patients with Fabry disease. As reported by Mignani (Mignani, R. & Cagnoli, L., Enzyme replacement therapy in Fabry's disease: recent advances and clinical applications, *J Nephrol.*,

17(3):354-363), enzyme replacement therapy with agalsidase α (a recombinant α-galactosidase obtained from human fibroblast) and agalsidase β (a recombinant α-galactosidase obtained from Chinese hamster ovary) resulted in reduction in storage of the glycosphingolipids' substrate from several organs and tissues and, consequently, improved signs and symptoms of Fabry's disease. Increase in the mean creatinine clearance, significant improvement in the acroparaesthesias and in the hypohidrosis after 12 months of therapy with purified α-galactosidase was described by Bongiorno *et al.* (Bongiorno, M.R., *et al.*, Fabry disease: enzyme replacement therapy, *J Eur Acad Dermatol Venerol.*, 2003, 17(6):676-679). The treatment the Fabry's disease patients with agalsidase β demonstrated the long-term efficacy (30 months) of the treatment, including a continuous decrease in plasma GL-3 levels, sustained endothelial GL-3 clearance, stable kidney function and a favorable safety profile (Wilcox, W.R., *et al.*, Long-term safety and efficacy of enzyme replacement therapy for Fabry disease, *Am J Hum Genet.*, 2004, 75(1):65-74).

It is overall concluded that elevated levels of α-galactosidase A lead to significant clinical benefits in patients with Fabry disease (Beck, M. *et al.*, Fabry disease: overall effects of agalsidase α treatment, *Eur J Clin Invest.*, 2004, 34(12):838-844). These publications along with numerous analogous art undoubtedly establish a correlation between the elevated levels of alpha-galactosidase A in Fabry-diseased patients and their positive outcome. As such, the correlation between the disclosed expression levels of alpha-galactosidase A in Fabry-diseased mice and the alleviation of the symptoms of the disease is a well known phenomenon to a skilled artisan. "The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art...." *See, Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795,804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999). "Because an enabling disclosure by definition turns upon the objective understanding of a skilled artisan, the enablement requirement can be met by reference to the knowledge of one of ordinary skill in the relevant art." *See*, MPEP § 2321, § 2340.

The Examiner further argues that the interpretation of the results obtained in mice is inadequate when applied to humans (Office Action, page 8, "humans are not simply large mice"). This rejection is traversed. Reconsideration is respectfully requested.

The fact cannot be ignored that any candidate for a drug is initially tested in animals. Mice are primary targets for testing, and, as such, numerous lines of mice with different deficiencies have been created to serve as models for various diseases. One example is a mouse model of Fabry's disease, which is a valuable instrument for exploring the therapeutic

strategies for patients with this condition. The knockout (Fabry) mice display a complete lack of α-galactosidase A activity. Ultrastructural analysis revealed concentric lammelar inclusions and accumulation of substrate in the kidneys as well as in the cultured fibroblasts. Lipid analysis showed a marked accumulation of ceramidetrihexoside in the liver and in the kidneys. These findings indicate the similarity of the pathological process in the mutant mice and in patients with Fabry disease (Ohshima, T. *et al.*, α-Galactosidase A deficient mice: a model of Fabry disease, *Proc Natl Acad Sci* USA, 1997, 94(6):2540-2544). Therefore, results obtained on mice models are interpretable to humans, undoubtedly taking into consideration human safety and efficacy trials.

Finally, the Examiner alleges that the specification does not provide sufficient guidance as to how to use a DNA plasmid comprised of an expression cassette comprising a myosin light chain enhancer, a viral promoter, and a nucleic acid sequence encoding any polypeptide of therapeutic use. This rejection is traversed. Reconsideration is respectfully requested.

The specification provides ample support for how to make and use the constructs. For example, on pages 3-7 and in the Examples 1 and 2 (pages 11-22) the specification teaches in details how to use claimed DNA constructs, the influence of different combinations of constructs, promoters and enhancers on the expression of the α-galactosidase gene, and how to transfer the α-galactosidase gene into a mouse model of Fabry's disease. Such an extensive disclosure provides significant guidance to a skilled artisan of how to make and use the claimed invention without undue experimentation, as all of the elements of the claimed method are described in great detail.

Accordingly, based on aforementioned discussion, it is respectfully requested that the rejection of claims 31-35, 40-42, 51, 58-62, 67-69 and 78 under 35 U.S.C. §112, first paragraph be withdrawn.

III. REJECTION UNDER 35 U.S.C. §112, 2nd PARAGRAPH

Claims 31-35, 40-42, 51, 58-62, 67-69 and 78 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner argues that claims 41, 42, 68 and 69 are indefinite in their recitation of the phrase "further comprising...genomic sequences flanking said expression cassette" since the expression cassettes implicitly comprise genomic sequences; thus, it is not clear how the

limitation further limits the base claim. Additionally, the Examiner argues that claims 31, 58 and their dependent claims are incomplete since the method steps do not clearly relate back to the preamble which recites a "method of treatment", do not recite an object to which the administration step is directed to, nor any recited step relating to "treatment" and, therefore merely recites an intended use and accorded no patentable weight.

With respect to the first point of the rejection, claims 41, 42, 68 and 69 have been amended to delete the word "further" and, as such, to define the vector as comprising fish or mammalian genomic flanking sequences (claims 41 and 68) or viral genomic flanking sequences (claims 42 and 69). Thus, claims 41 and 42 further limit claim 31. Similarly, claims 68 and 69 further limit claim 58. As such, these claims are proper dependent claims and definite in particularly pointing out and distinctly claiming the invention. Accordingly, it is respectfully requested that the rejection of claims 41, 42, 68 and 69 under 35 U.S.C. §112, second paragraph be withdrawn.

With respect to the second point of rejection, Applicant has amended claims 31 and 58 to recite in pertinent part: "A method for treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency, said method comprising administering to a subject in need thereof an effective, non-toxic amount of...". As amended, claims 31 and 58 and their dependent claims are complete and, therefore, definite. Accordingly, it is respectfully requested that the rejection of claims 31-35, 40-42, 51, 58-62, 67-69 and 78 under 35 U.S.C. §112, second paragraph be withdrawn.

IV. REJECTION UNDER 35 U.S.C. §103(a) OVER GOLDSPINK IN VIEW OF JEANG

Claims 31-35, 40-42 and 51 are rejected under 35 U.S.C. 103(a) as obvious over Goldspink *et al.*, (WO 94/28151, hereinafter, "Goldspink") in view of Jeang *et al.* (Molecular and Cellular Biology, 1984, 4:2214-2223, hereinafter "Jeang"). In particular, the Examiner argues that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the truncated rabbit β-cardiac myosin heavy chain promoter with the promoter from CMV IE94 to obtain an expression vector that expresses high levels of F[illegible]or VIII in mammalian muscle cells. This rejection is traversed. Reconsideration is respe[illegible]

To establish a pr[illegible]der 35 U.S.C. §103(a), the Examiner must show that all the l[illegible]present in all references cited

against them (*In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), MPEP § 2143.03) as well as the cited art alone or in combination should suggest or motivate arriving at the claimed invention (*In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984); MPEP § 2143.01). Applicant respectfully submits that in the instant case these requirements are not met.

The Goldspink reference discloses a recombinant nucleic acid construct comprising a mammalian myosin heavy chain promoter, a nucleic acid encoding a signal sequence and a nucleic acid encoding a functional blood clotting protein, Factor VIII, useful for the treatment of haemophilia. The instant invention is related to a method of treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency using an expression cassette comprised of a myosin light chain enhancer, a viral promoter and a polynucleotide sequence encoding an α-galactosidase gene. As admitted by the Examiner (Office Action, page 15), Goldspink does not teach the use of a viral promoter. Thus, the reference does not teach each and every limitation of the instant claimes.

Contrary to the Examiner's assumption that the teachings of Jeang remedy the deficiency of the Goldspink, they do not. Jeang discloses the expression of a specific viral protein in nonpermissive rodent cells after cytomegalovirus (CMV) strain infection. The ordinary fact that the CMV gene can be expressed in mammalian cells does not mean that the CMV gene could be successfully incorporated into the expression cassette of the instant invention. Thus, nothing in Jeang teaches or suggests the expression cassette as instantly claimed.

It is well-known in the art that studies on the regulatory functions of specific CMV proteins are complicated by the absence of temperature-sensitive mutants, the simultaneous presence of input viral capsid components, and the closely linked sequential expression of numerous viral polypeptides during a normal infection cycle. Additionally, it is known that vectors' viral components can provoke immune and/or toxic reactions, produce pathogenic replication-competent viruses based on recombination events and trigger an undesired activation of potential oncogenic sequences because of integration in undefined regions of the genome (*see*, in Abdallah *et al.*, page 1, col. 2, 1st paragraph, cited by the Examiner). Thus, the state of the art, in fact, teaches away from the use of a viral promoter in the claimed expression cassette. Therefore, nothing in Jeang would motivate a skilled artisan to substitute the truncated rabbit β-cardiac myosin heavy chain promoter disclosed in Goldspink with the viral promoter from CMV. Accordingly, the combined teachings of Goldspink and Jeang do not render the instant invention obvious. Therefore, it is respectfully requested that the

rejection of claims 31-35, 40-42 and 51 under 35 U.S.C. 103(a) be withdrawn.

V. REJECTION UNDER 35 U.S.C. §103(a) OVER GOLDSPINK IN VIEW OF FENJVES AND ABDALLAH

Claims 58-62, 67-69 and 78 are rejected under 35 U.S.C. 103(a) as obvious over Goldspink *et al.*, ("Goldspink") in view of Fenjves *et al.* (Proc Natl Acad Sci USA, 1989, 86:8803-8807, hereinafter "Fenjves") and Abdallah *et al.* (Biol Cell, 1995, 85:1-7, hereinafter "Abdallah"). In particular, the Examiner argues that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to insert the cDNA sequence of human apolipoprotein E, taught by Fenjves, into the expression plasmid taught by Goldspink, in view of the Abdallah's disclosure This rejection is traversed. Reconsideration is respectfully requested.

As discussed in section IV above, Goldspink discloses a recombinant nucleic acid construct useful for the treatment of haemophilia, *i.e.*, comprising Factor VIII coding region as a functional polynucleotide. The constructs also include mammalian myosin heavy chain promoter and a signal sequence. The instant invention relates to a method of treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency using an expression cassette comprised of polynucleotide sequence encoding an α-galactosidase gene. Although Goldspink teaches that the disclosed vector is used to express Factor VIII, he does not teach that the constructs can be used to express other proteins (as admitted by the Examiner on page 17 of the Office Action), let alone, proteins that would be useful for the treatment of an α-galactosidase A deficiency.

The Fenjves reference does not cure the deficiencies of Goldpink. Rather, Fenjves focuses on systemic distribution of apolipoprotein E (apoE) secreted by grafts of epidermal keratinocytes (*see*, in Fenjves, page 8805, col. 2, 1st paragraph). As Fenjves neither suggests the claimed invention nor remedies the deficiencies of Goldspink, nothing in Fenjves suggests or motivates a skilled artisan to modify the teachings of Goldspink by inserting the cDNA sequence of apoE into the expression plasmid taught by Goldspink with a reasonable expectation of success.

Abdallah teaches the advantages and drawbacks of viral and non-viral gene transfer as well as three non-viral delivery systems: cationic lipids, cationic polymers and free DNA. The disclosed drawbacks in using vectors' viral components in gene transfer procedure, as discussed in section IV above, in fact teach away from the claimed invention. As such, the

reference's disclosure is irrelevant, hence, the combination of references, suggested by the Examiner, is improper.

Therefore, it is respectfully submitted that the teachings of Goldspink, Fenjves and Abdallah, viewed alone or in combination, do not render the claimed invention obvious. Accordingly, it is respectfully requested that the rejection of claims 58-62, 67-69 and 78 be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully submits that claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97 and 98 satisfy all the criteria for patentability and requests to consider the subject application towards allowance.

No fees other than the extension of time fees are believed to be due. However, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013 (referencing the Attorney Docket No. 10103-004-999).

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